Carcinogenicity of human papillomaviruses

Vincent Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi
WHO International Agency for Research on Cancer

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In February, 2005, 25 scientists from 13 countries (panel) met at the International Agency for Research on Cancer (IARC; Lyon, France) to reassess the carcinogenicity of human papillomaviruses.[1] Persistent infection with a carcinogenic human papillomavirus is found in virtually all cases of cervical cancer—the second most common cancer in women worldwide, with almost 471 000 new cases and 233 000 deaths in 2000.[2] About 80% of cases occur in developing countries that do not have adequate screening programmes.

Human papillomaviruses infect human mucosal and cutaneous tissues. The prevalence of genital human papillomavirus infection varies between countries (1–40% in women). Although most infections resolve within 2 years, persistent genital human papillomavirus infection can lead to cancer, including cervical cancer. Infection with human papillomavirus is reliably recorded by use of assays that detect viral DNA. Studies have associated specific types of human papillomavirus with cervical cancer or cervical intraepithelial neoplasia stage 3 (CIN3), a precursor to invasive cervical cancer. Prophylactic vaccination against human papillomavirus infection might be realised shortly. A more distant goal is to develop therapeutic vaccines as adjuvant treatment for infections or cancers associated with human papillomavirus.

Animal papillomaviruses can be carcinogenic in their natural hosts, but they do not infect humans, and human papillomaviruses do not infect animals. Data for animal papillomaviruses were reviewed by the Working Group but were not considered in the assessments.

Epidemiological data from case-control studies, prospective cohort studies, and case series confirm the carcinogenicity of human papillomavirus types 16 and 18 in the cervix. In addition, findings from such studies show that infection with human papillomaviruses 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 66 can lead to cervical cancer. For human papillomavirus 16, data show a causal role in cancer of the vulva, vagina, penis, anus, oral cavity, and oropharynx, and some association with cancer of the larynx and periungual skin. Human papillomavirus 18 is also associated with cancer at most of these sites. Types 6 and 11 are not implicated in the development of cervical cancer, but are associated with squamous-cell carcinoma of the larynx and with uncommon Buschke-Löwenstein tumours in the vulva, penis, and anus. Several human papillomavirus types of the genus beta are associated with squamous-cell carcinoma of the skin. Data for this association is strong in patients with Epidermodysplasia verruciformis, but less so in the general population. Human papillomaviruses might have a role in squamous-cell carcinoma of the conjunctiva, but no conclusion could be reached for cancer of the oesophagus, lung, colon, ovary, breast, prostate, urinary bladder, or nasal and sinonasal cavities.

Important cofactors in cancer associated with human papillomavirus infection include coinfection with chlamydia or HIV, smoking, and parity (eg, >3 children); the role of hormonal contraceptives and nutrients is unclear.

Viral proteins E6 and E7, which are selectively expressed in human-papillomavirus-associated cancers, have potent transforming activity in tissue culture and tumorigenic action in transgenic mice. Of particular importance, these proteins promote genetic instability through induction of cellular proliferation, disruption of cell-cycle checkpoints, inhibition of apoptosis, and induction of telomerase.

The Working Group concluded that human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 are carcinogenic to human beings. Human papillomaviruses 6, 11, and some human papillomavirus types of the genus beta (including types 5 and 8) are possibly carcinogenic to human beings. The Working Group noted that the human papillomavirus types classified as carcinogenic to human beings can differ by an order of magnitude in risk for cervical cancer, and cautioned that the design of screening tests for human papillomavirus must consider important differences between viral types and other societal factors.

The authors declare no conflicts of interest.

1 IARC. IARC monographs on the evaluation of carcinogenic risks to humans, volume 90, human papillomaviruses. Lyon: (in press).

2 Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001; **37** (suppl 8): S4–S66.